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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,055	03/01/2001	Christian Belmant	BE 8992	6944

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,055	BELMANT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-89,96-99,103-114 and 116-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *96,97,116 and 117* is/are allowed.

6)☐ Claim(s) *107-114 and 119* is/are rejected.

7)☒ Claim(s) *85-89,98,99,103-106,118 and 120* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 9/9/05.

Claims 94, 95, 101, and 102 were canceled and claim 120 was added as requested.

Claims 85-89, 96-99, 103-114, and 116-120 remain pending and under consideration in this Office Action.

The Declaration under 37 CFR 1.132 of Jean-Jacques Fournie was entered on 9/9/05, and completely considered as discussed more fully below.

The previously indicated allowability of claim 98 and dependents 99 and 103-106 is withdrawn in view of minor objections to claim 98.

Claim Objections

Applicant's amendments were sufficient to overcome the previous objection to claim 103.

The listing of the claims is objected to because it contains a list of structures between claims 97 and 98 that are not part of any claim.

Claim 85, and dependents 86-89, 118, and 120, are objected to because claim 85 contains a period immediately before item '(c)'.

Claim 98, and dependents 99 and 103-106, are objected to. Insertion of --a-- immediately before "Tγ9δ2" in claim 98 is suggested. Also, deletion from item 'b)' of the second instance of "a compound of the formula:" in claim 98 is suggested.

Insertion of --and-- immediately after "cation," in claims 107 and 114 is suggested.

Rejections Withdrawn

Applicant's amendments were sufficient to overcome the rejection of claims 97-114, 116, and 117 under 35 USC 112, second paragraph.

Applicant's amendments were sufficient to overcome the rejection of claims 97-114 under 35 USC 112, first paragraph for lack written description.

The rejection of claims 85-89 and 118 under 35 USC 112, first paragraph are withdrawn in view of Applicant's amendment limiting these to *in vitro* methods.

The rejection of claim 104 under 35 USC 112, first paragraph is withdrawn after further consideration and in view of Applicant's arguments. A claim to a composition needs only one enabled use. The composition of claim 104 could be used to expand gamma delta cells in vitro for diagnostic purposes. The claim recites no in vivo intended use. The fact that the composition is in a form that can be topically administered does not mean that it must be applied in vivo. In fact the composition could be applied "topically" to cells that have been pelleted by centrifugation and which are then resuspended in a solution containing the composition. Addition of the solution to such cells would amount to topical application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 107-114, and 119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods of activating Tγ9δ2 lymphocytes, does not reasonably provide enablement for activating Tγ9δ2 lymphocytes in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors.

Nature of the invention and Breadth of the claims

Claims 107-114, and 119 are drawn to methods of activating Tγ9δ2 lymphocytes, in vitro or in vivo. The specification teaches that Tγ9δ2 lymphocytes may be activated in vitro for the purpose of studying the activated cells. See page 20, lines 1-6. It is clear from the state of the prior art of record that activated Tγ9δ2 were objects of research interest prior to the time of the invention. When used in vivo, the method may be for therapeutic use (page 20, lines 6 and 7) or for diagnostic use (page 20, lines 29-32). The scope of therapeutic uses is broad and embraces both preventative and curative embodiments (page 20, lines 29-32). The scope of treatable diseases includes conditions belonging to the group comprising cancers, infectious diseases, in particular mycobacterial infections (leprosy, tuberculosis etc.), parasitic conditions (malaria etc.), and pathological immunodeficiency syndromes (MDS etc.) The specification also

teaches that Tγ9δ2 cells can be activated ex vivo and then used for therapy. Use activated T-cells for therapy is known in the art as adoptive immunotherapy.

State of the prior art

Yamaguchi et al (J. Immunol. Met. 205(1): 19-28, 6/23/97) taught that gamma delta T cells make up no more than 10% of peripheral blood mononuclear cells, but appear to play an important role in host defense against tumor growth. In order to evaluate their functional activity against tumors, large quantities of cells are required. Yamaguchi taught a method of producing large quantities of gamma delta T cells by isolating them inducing TCR/CD3-mediated signal transduction by contacting the cells with an anti-CD3 antibody and IL-2. Yamaguchi noted that this method may make it possible to produce sufficient numbers of gamma delta T cells for clinical trials of anti-tumor adoptive immunotherapy. See abstract. Thus it was recognized in the art at the time of the invention that obtaining a sufficient number of gamma delta T cells was an obstacle to adoptive immunotherapeutic methods relying on these cells. Although Yamaguchi taught a potential solution to this problem, it was clear that those of skill in the art would not be convinced that the teachings of Yamaguchi were sufficient to solve the problem. For example, Janssen et al (J. Immunol. 146(1): 35-39, 1/1/91) taught that stimulation of gamma delta cells with anti-CD3 antibody and IL-2 led ultimately to cell death through apoptosis, thus calling into question the usefulness of this method for expanding gamma delta cells to the numbers needed for therapeutic purposes. Indeed Lopez et al (Blood 96(12): 3827-3837, 12/1/2000) taught that the exploitation of gamma delta T cells for therapeutic ends remained largely unrealized because of the extreme

difficulty in obtaining sufficient quantities of these cells. Lopez noted that while treatment of gamma delta T cells with anti-CD3 or anti-TCR antibodies is an attractive means of expanding these cells, this method results in apoptosis, thereby presenting a serious obstacle to developing approaches to incorporate gamma delta T cells into any form of adoptive immunotherapy. See page 3827, column 2, lines 2-18. Lopez concluded, [w]hether γδ-T cells have therapeutically exploitable biologic properties such as antiviral, antitumor, or hematopoietic stem cell graft-facilitating effects, remains to be determined. See page 3836, column 2, lines 5-8. Lopez indicates that amounts of cells far in excess of 10^9 would be needed for therapeutic purposes. See page 3836, lines 7-17.

A search of the prior art revealed no instances of complete disease prevention or cure through the use of Tγ9δ2 cell adoptive immunotherapy.

Unpredictability in the art

The teachings of Janssen (1991) and Lopez (2000) above show that at the time of the invention, the art of adoptive immunotherapy using Tγ9δ2 cells was highly unpredictable, essentially because of the technical difficulty in obtaining sufficient numbers of apoptosis-resistant cells. Furthermore, even if a sufficient number of cells could be obtained, it was not predictable that these cells would be useful for any therapeutic method. See page 3836, column 2, lines 5-8.

Guidance and exemplification in the specification

The specification teaches how to make phosphoepoxide compounds and demonstrates that they can be used to stimulate proliferation of Tγ9δ2 cells in the

presence of IL2. See e.g. pages 25-33 of the specification. The specification fails to teach the production of quantities of Tγ9δ2 cells approaching 10^9, and fails to provide any information as to the mechanism of Tγ9δ2 cell proliferation, or any apoptotic effects of phosphoepoxide-mediated mitogenesis. The specification provides no working example of any therapeutic use of the clamed methods. The specification also provides no guidance as to how to use the claimed methods for any in vivo diagnostic purpose.

Amount of experimentation required

Due to the unpredictable nature of the art of Tγ9δ2 cell adoptive immunotherapy, the recognition in the art that larger numbers of Tγ9δ2 cells were required for therapy than could be produced by existing methods, the failure of the specification to teach how to produce sufficient numbers of cells for therapeutic purposes, and whether or not these cells are subject to apoptosis, particularly in view of their treatment with IL2, one of skill in the art would have to perform undue experimentation to use the claimed compositions for therapeutic purposes as required by the claims. In addition, although the specification teaches that the claimed methods may be used in vivo for diagnostic purposes, the specification gives no guidance or examples in this regard, and it is not immediately apparent how one could use the claimed methods for diagnostic purposes in vivo. This rejection can be overcome by limiting the claimed methods to the scope of in vitro. Claims 101 and 102 are included in this rejection because they are compositions which are adapted to be used in vivo.

Response to Arguments

Applicant's arguments filed 9/9/05, and the declaration of Jean-Jacques Fournie, have been fully considered but are unpersuasive.

Applicant responds to the rejection at page 18 of the response. Applicant asserts the claims have been limited to the compound of Formula 2, and that the declaration of Dr. Fournie provides evidence that the administration such compounds in vivo can lead to an expansion/activation of lymphocytes. The declaration reports results from an experiment in which the compound of formula 2 (referred to as EpoxPP) was administered in equal amount to 4 cynomolgus monkeys, and a placebo was administered to four control cynomolgus monkeys. The percent of CD3 positive cells comprising Vδ2 antigens in whole blood samples from the animals was determined by a three color flow cytometry test, apparently designed to detect Vδ2, CD69/CD25, or CD3 antigens. Blood was collected on days 0, 7, 14, 29, and 44 after EpoxPP administration, and Fig. 1 shows data from each collection. There is no statistical analysis of the data.

Dr. Fournie declared that Fig. 1 shows a clear expansion of gamma delta cells in monkeys 31 and 32, particularly on days 29 and 44. This is unpersuasive because the sample size is very small, and the statistical significance of the data is unknown. Note that two monkeys (29 and 30) that received EpoxPP generally showed a lower percentage of CD3/ Vδ2+ cells than the placebo-treated controls, whereas two monkeys (31 and 32) generally showed a greater percentage. So it appears that half the treated monkeys showed a decrease in Vδ2+ cells, whereas half showed an increase. If one

attempts a quantitative analysis of the data on day 29, it appears that on average the control monkeys generally had about 1.3 times as many Vδ2+ cells on day 29 as on day 0, whereas the treated monkeys on average had about 1.6 times as many on day 29 as on day 0. It is unclear if this small difference is significant, particularly in view of the fact that the percentage of Vδ2+ cells in individual monkeys on day 0 of the experiment ranged from about 0.3% to 3%, indicating that a 10-fold difference in the amount of Vδ2+ cells from animal to animal was not statistically significant. Finally it is unclear from the data whether or not a sufficient number of cells can be activated to have any therapeutic effect. Note that Lopez (2000, cited above) indicated that amounts of cells far in excess of 10^9 would be needed for therapeutic purposes. See page 3836, lines 7-17. Given the lack of statistical significance of the data, and the failure to show that therapeutic amounts of gamma delta cells could be produced in vivo, the opinion of Dr. Fournie unpersuasive.

In a further experiment to test the ability to expand Vδ2+ cells ex vivo I IL-2, blood cells drawn from the monkeys described above were cultured for about 10 days in medium alone, medium + IL-2, or medium + IL-2 + EpoxPP. Data from the medium + IL-2 and medium + IL-2 + EpoxPP experiments are presented in Figs 2 and 3 respectively. The experiment is described at page 3 of the declaration. Dr. Fournie concluded that there was no difference in Vδ2+ cells taken from between control animals and EpoxPP-treated animals when the cells were cultured in medium containing only IL-2, whereas Vδ2+ cells taken from monkeys 31 and 32 on days 29 and 44 showed a "significant" expansion when cultured in the presence of IL-2 and EpoxPP.

The opinion of Dr. Fournie is unpersuasive as it applies to the enablement rejection above. The Examiner has indicated that the specification is enabling for the expansion of isolated gamma delta cells by addition of EpoxPP for diagnostic purposes. The issue with regard to the enablement rejection above is whether or not one can obtain sufficient gamma delta cells by in vivo expansion to perform therapy in vivo. It is not clear how the second experiment addresses that issue. The Office has established that therapeutic ex vivo stimulation of gamma delta T cells for therapeutic use (adoptive immunotherapy) is highly unpredictable. The claimed method of in vivo activation of these cells is subject to at least the same level of unpredictability established for the ex vivo method of adoptive immunotherapy, as well as the increased unpredictability attending the direct administration of the compositions to non-isolated cells in vivo. By comparison to adoptive immunotherapy, this in vivo approach is even more unpredictable because of factors such as the unknown effects on the claimed compounds of in vivo metabolism, and the unknown effects of dilution of the compounds relative the ex vivo system. Again, it is unclear how the in vitro experiment set forth at page 3 of the declaration and in Figs 2 and 3 is relevant to this issue.

Conclusion

Claims 96, 97, 116, and 117 are allowable.

Claims 85-89, 98, 99,103-106, 118 and 120 are objected to.

All claims are free of the prior art of record.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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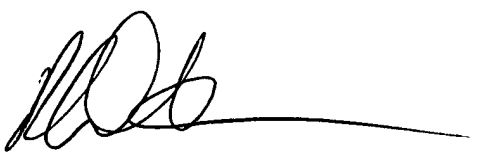

Richard Schnizer, Ph.D.